Cardiovascular Therapy: Open Access

Altura et al., Cardiovasc Ther 2017, 2:2

Short Communication OMICS International

Why is Cardiac Morbidity and Mortality Greater Around Christmas, New Year's, Monday Mornings and in the Morning Hours: Potential Roles of Unrecognized Ionized Hypomagnesemia and Release of Ceramides?

Burton M Altura[1-5]*, Joshua Burack[6], RF Tranbaugh[6], Z Zisbrod[6], JN Cunningham[6], Nilank C Shah[1,5], Gatha J Shah[1], Lawrence M Resnick[7] and Bella T Altura[1,3-5]

[1]*Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, New York, USA*
[2]*Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York, USA*
[3]*Center for Cardiovascular and Muscle Research, State University of New York Downstate Medical Center, Brooklyn, New York, USA*
[4]*School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, New York, USA*
[5]*Bio-Defense Systems, Inc, Rockville Center, New York, USA*
[6]*Department of Surgery, State University of New York Downstate Medical Center, Brooklyn, New York, USA*
[7]*Department of Medicine, Cornell University School of Medicine, New York, USA*

Introduction

There is a growing incidence of lethal cardiac events around Christmas, New Year's and in the morning hours from 4:00 to 10:00 a.m. which is well-established in the USA and in The Southern Hemisphere [1-7]. In addition, many cardiac deaths often occur on Mondays with no satisfactory explanation [2,3]. Many of these deaths are, for the most part, unexplained and listed as "death from "natural causes". Although in the USA, the deaths which occur around Christmas and New Years happen in the cold –winter months, this does not account for many cardiac incidences which occur throughout the year in the early a.m. hours or on Mondays.

A number of explanations have been offered to explain the higher morbidities and mortalities at these special times of the year, morning hours and on Mondays, such as emotional stresses, too much ingestion of alcoholic beverages, improper medical facilities, diet, and/or changes in the physical environments [1-7].

Role of Magnesium in Cardiac Morbidity and Mortality

Ever since our laboratories first reported that magnesium (Mg) deficiency results in vasospasms of small and large coronary arteries, and that these events could be responsible for a great deal of sudden death ischemic heart disease (SDIHD) [8,9], a number of clinical studies have appeared which have confirmed and extended these findings [10-15]. We originally speculated that low dietary Mg intake and /or errors in Mg metabolism could be responsible for a large number of sudden cardiac deaths (SCD) and heart attacks in the Western world [8, 9,16].

In the early 1980's, some clinical studies appeared which suggested that of all electrolytes measured in the blood of hospitalized patients, total serum magnesium (Mg) levels often showed lowered levels, e.g., from 80-50% of normal [17-21]. However, in general, patients admitted to the intensive or coronary care units often demonstrated 60-30% of normal total blood levels of Mg [21-27]. When the blood/sera/plasma from these patients are examined for ionized Mg levels, in addition to the latter measured total Mg levels, these numbers rise to 80-70% in the patients admitted to intensive and coronary care units [26,27]. In addition, the red blood cells obtained from these patients are severely deficient in ionized Mg (e.g., 60-40% of normal; Resnick, Altura, and Altura, unpublished studies). Why is it so important to measure ionized Mg levels, not only total blood Mg levels?

Mg is a co-factor for more than 500 enzyme systems, and is the second most abundant intracellular cation after potassium [28]. It is critical in numerous physiological, cellular and biochemical functions and systems, running the gamut from hormone-receptor binding, transmembrane fluxes of cations and anions, cellular energy generation, muscle contraction, regulation of DNA and RNA structure, regulation of lipid and carbohydrate metabolism, regulation of plasma lipid levels (i.e., cholesterol, triglycerides, and LDL-cholesterol), regulation of cell and tissue growth, nerve conduction, diverse cardiac functions and cardiac stability, control of vasomotor tone and distribution of blood flows to all organ systems, and cell death (i.e., apoptosis and necroptosis), among many others [28-38]. Mg is depleted in normal methods of food preparation (e.g., boiling, frying, etc.) and processing [39].

The daily intake of Mg has been declining since 1900, from where it was about 500-600 mg/day to about 150-225 mg/day, in many USA and European geographic regions, at the present time [40-42]. Mg is known to exist in three forms; free or ionized, complexed, and protein – bound [26]. These three fractions constitute the total serum and cell Mg [26]. In addition, up until our studies, there were no reliable methods to measure ionized Mg on whole blood, serum , and plasma rapidly (within 1-2 min) in the OR and critical-coronary care units [27].

Of almost 100 patients who were admitted for emergency coronary artery bypass surgery (CABS), at our hospitals (e.g., University Hospital and Kings County Hospitals), 88% of them exhibited significantly lowered levels of serum ionized Mg^{2+}, but not necessarily total serum Mg levels [27,43-46]. Of those who were admitted on Holidays, such as Christmas or Thanksgiving, or in the morning hours (i.e., from 2:00 – 7:00 AM), we observed the lowest serum levels of Mg^{2+} (i.e., from 0.40 – 0.52 mM vs. 0.57-0.70 mM-controls, $p<0.001$). Patients admitted on Monday mornings (i.e., from 2:00 – 9:00 AM) for CABS exhibited, on average 0.48 ± 0.06 mM vs 0.67 ± 0.03 mM ($p<0.01$). For the most part, many (about 55%) of these CABS patients exhibited near, normal total serum Mg levels.

When we mimicked these, lowered serum Mg^{2+}, *in vitro*, using

***Corresponding author:** Dr. Burton M Altura, Department of Physiology & Pharmacology, SUNY Downstate Medical Center, 450 Clarkson Ave, Brooklyn, New York 11203, USA, Tel: 718-270-2194; E-mail: baltura@downstate.edu

Received: June 16, 2017; **Accepted:** June 26, 2017; **Published:** June 30, 2017

Citation: Altura BM, Burack J, Tranbaugh RF, Zisbrod Z, Cunningham JN, et al. (2017) Why is Cardiac Morbidity and Mortality Greater Around Christmas, New Year's, Monday Mornings and in the Morning Hours: Potential Roles of Unrecognized Ionized Hypomagnesemia and Release of Ceramides? Cardiovasc Ther 2: 118.

isolated, normal canine, baboon, monkey, human or piglet coronary/cerebral arteries, they went into different degrees of vasospasm which could only be relaxed with increased levels of Mg^{2+}, not with calcium channel blockers or a variety of commonly-used vasodilator drugs [8,9,16,47-57]. The artificially-lowered levels of Mg^{2+} also resulted in potentiation of the contractile actions of all types of circulating neurohormonal vasoconstrictor agents (e.g., catecholamines, angiotensin II, serotonin, and a variety of peptides including vasopressin, etc.) [8,9,16,47-58].

From our studies, we believe the data are consistent with the hypothesis that human subjects admitted for emergency CABS on major holidays, in the morning hours , or on Monday mornings not only demonstrate abnormally low Mg^{2+} levels but most likely are predisposed to vasospasm of the coronary and cerebral arterial vessels which would result in increased morbidity and mortality. So, it makes eminent sense that human subjects, worldwide, would be predisposed to increased morbidity and mortality on holidays such as Christmas, New Year's Day and Monday mornings. An important factor involved in these predilections, at these various times of the year, are also most likely due to the excess drinking of alcoholic beverages, coffee and sodas (with caffeine), which have been shown to rapidly deplete vascular smooth muscle, cardiac muscle and endothelial cells of intracellular levels of Mg^{2+}[59-74]. In addition, since many people get heart – burn after heavy meals, they have a tendency to ingest proton-pump inhibitors which also can reduce Mg levels [46]. One must also consider the possibility that a number of the subjects dying from SDIHD and SCD may have been on long-term treatment with cardiac glycosides and/or thiazides, certain antifungal agents (i.e., amphotericn B), aminoglycosides (e.g., gentamicin, tobramycin), loop diuretics (e.g., furosemide), immunosuppresents(e.g., cyclosporine, sirolimus), or even certain chemotherapeutic agents (cisplatin, amsacrine), all of which deplete the body of Mg; potential interactions with drinking of alcoholic beverages and/or caffeine –beverages would tend to reinforce (and potentiate) the tendency for considerable, rapid Mg depletion [20-22,30-33,36,74]. Unfortunately, such interactions have not been a focus of any epidemiological studies to our knowledge.

The cellular, biochemical, and molecular mechanisms of how lowered cellular levels of Mg^{2+} cause vasospasm and decreased peripheral, coronary, and cerebral blood flows, inflammation, ischemic events , atherogenesis, and diverse forms of cell death have been a long-time focus of our laboratories which are presented and discussed elsewhere [16,29,31,32,34,35,37,38,47-64,75-98]. In this context, using proton –nuclear magnetic spectroscopy (NMR), P^{31} –NMR, and brand-new ELISA assays, we have found that low levels of extracellular Mg^{2+} ($[Mg^{2+}]_0$) rapidly generated ceramides and other sphingolipids [32,34,82-89,91-93,96-98] which, heretofore, were totally unknown as potential causal factors in SDIHD, sudden cardiac death (SCD), congestive heart failure (CHF) and coronary artery disease (CAD) . This work led us to hypothesize that dietary deficiency and/or inborn metabolic-induced deficiency of Mg could result in increased morbidity and mortality from coronary and cerebral arterial vasospasms. But, how would generation of ceramides and/or other sphingolipids(e.g., sphingosine; sphingosine-1-phosphate) result in susceptibility to SDIHD, SCD, CHF, and CAD?

Ceramides are sphingolipids known to be released as a consequence of sphingomyelinases (SMase) acting on sphingomyelin (SM), a component of all cell membranes, or as a consequence of the activation of serine palmitoyl transferase 1 and 2 (SPT 1 and SPT 2) (a *de novo* synthetic pathway) [99-101]. Ceramides are now thought to play important roles in fundamental processes such as inflammation, angiogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunologic responses, excitation-coupling events in smooth muscles, and cell death (i.e., apoptosis) [99-110]. SPT 1 and SPT 2 are the rate-limiting enzymes in the biosynthesis of *de novo* sphingolipids [99,100]. More than 25 years ago, it was first demonstrated that SPT activity was increased in aortas of rabbits fed a high cholesterol diet [111]. A short time (i.e., 1990) after these latter studies were published, two of us showed that dietary deficiency of Mg, in levels found in Western diets, vastly increased atherosclerotic plaque formations in rabbits fed high-cholesterol diets, whereas high dietary levels of Mg inhibited plaque formations [78]. We also noted that early intervention with oral Mg administration reversed the growth and intensity of the plaque formations. SPT is a heterodimer of 53-kDa SPT-1 and SPT-2 subunits [112,113], both of which are bound to the endoplasmic reticulum [114]. An upregulation of SPT activity has been hypothesized to play a role in apoptosis [115]; cell death events which take place in atherogenesis [116-118].

Recently, several of us have reported that Mg deficient (MgD) diets given to rats for only 21 days results in an upregulation of SMases, sphingomyelin synthase, ceramide synthase, SPT -1 and SPT-2 in a variety of cardiovascular tissues and cells as well as decreased levels of SM and phosphatidylcholine (PC) [34,37,85,86,88,91,93,94,119]. We also noted that MgD diets resulted in fragmentation of DNA [37,94], a release of mitochondrial cytochrome C (a result of leaky membranes) [88], an increased expression of apoptotic protease factor-1, an activation of caspase-3 (needed for apoptosis) [87], and upregulation of p53 [119], release of cytokines [91,120], activation of three different nitric oxide isozymes [89], activation of multiple protein kinase C isozymes [120], activation of mitogen-activated kinases (MAPKs) [63,121], activation of tyrosine kinases [121], activation of P-I-3 kinases [63,64] and upregulation of receptor -interacting kinases (e.g., RIPK1 and RIPK3) [38], all hallmarks of various stages of atherogenesis. When specific inhibitors of SMases and SPT (1 and 2) were utilized in primary cultures of vascular smooth muscle (VSM) cells, exposed to low $[Mg^{2+}]_0$ environments, we noted an inhibition of formation and release of ceramides, inhibition of release of cytochrome C, reduced expression of apoptotic protease factor-1, reduced expression of various PKCs, MAPKs, and NO as well as inhibition of release of cytokines, and inhibition of activation of caspase-3 and p53 [34,37,38, 87-89,91-98,119,120]. We believe, collectively, these new studies lend support to our hypothesis that generation and release of ceramides in MgD are pivotal molecules in the initiation of cellular and molecular events leading to inflammatory events and atherogenesis. The fact that we have found elevated ceramide levels in the sera of CABS patients who presented with CHF and CAD strengthens our hypothesis, particularly as the subjects that died of SDIHD and SCD on the holidays and on Monday mornings had the lowest serum levels of ionized Mg coupled to the highest serum levels of the ceramides.

Since we have demonstrated in both rats and rabbits, fed low Mg diets, that increased levels of ceramides are found in situ, in all chambers of the heart, aortae and coronary arterial blood vessels, and these manifestations were associated with increased plaque formations, elevated serum cholesterol, elevated LDL-cholesterol, and elevated trigycerides [35,37,78,96, 97,106], it is highly unlikely that these *in-vivo* manifestations are merely epiphenomena. Only time will -tell whether our hypothesis is correct. But, how could the risk of susceptibility, on holidays, morning hours, and Monday mornings, to SDIHD, SCD, and CAD be avoided or reduced?

Over the past 20 years, our laboratories have been investigating the utility of Mg-supplemented or naturally-occurring spring waters to avoid the potential pitfalls of dietary –induced MgD-states, thus reducing the risks of morbidities and mortality from SDIHD, SCD, and CHF . Our results, so far, bolster the idea that water intake (e.g., from tap waters, well waters, beverages using tap/well/spring , or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg^{2+}[87-89,91-98, 119,120,122]. A number of studies, done in our labs, indicate that most, if not all the cardiovascular manifestations observed in experimental animals (discussed above) found to be MgD can be avoided by supplementing drinking waters with appropriate amounts of Mg^{2+}. Supplementation of diets with adequate amounts of Mg, in our youth, should help to prevent the beginning of atherosclerotic plaques seen in growing children. The inclusion of adequate amounts of Mg in our diets , drinking waters, and beverages should cut-down, tremendously, the risks of SDIHD, SCD, CHF, and CADs, ,and, in the process, should greatly reduce the current 350 billion dollars/ year spent in the USA, alone, to treat cardiovascular diseases.

Acknowledgements

Some of the original studies summarized above were supported in part by research grants from The National Institutes of Health (NHLBI, ADAMHA, NIAAA, NIDA) to B.M.A. and B.T.A. We also received unrestricted grant support from The CIBA-GEIGY Corporation (Novartis Pharmaceuticals), The UpJohn Co., Sandoz Pharmaceuticals, and Bayer Pharmaceuticals, and from anonymous donors. While some of our studies were underway, our dear friend and esteemed colleague, Professor Lawrence Resnick, passed away. He will be sorely missed.

References

1. Phillips DP, Jarvinen JR, Abramson IS, Phillips RR (2004) Cardiac mortality is higher around Christmas and New Year's than at any other time: The holidays as a risk factor for death. Circulation 110: 3781-3788.
2. Cohen MC, Rohtia KM, Lavery CE, Muller JE, Mittleman MA (1997) Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 79: 1512-1516.
3. Phillips D, Baker GE, Brewer KM (2010) Christmas and New Year as risk factors for death. Soc Sci Med 71: 1463-1471.
4. Eagle K (2012) Hypothesis: holiday sudden death: food and alcohol inhibition of SULT 1A enzymes as a precipitant. J Appl Toxicol 32: 751-755.
5. Winkel G (2012) Sudden death in young Danes. Danish Med J 59: 84403.
6. Knight J, Schilling C, Barnett, Jackson R, Clarke P (2016) Revisiting the "Christmas Holiday Effect" in the southern hemisphere. J Am Hear Assoc 5: e005098.
7. Witte DR, Grobbee DE, Bots M, Hoes AW (2005) A meta-analysis of excess mortality on Monday. Eur J Epidemiol 20: 401-406.
8. Altura BM (1979) Sudden-death ischemic heart disease and dietary magnesium intake: Is the target site coronary vascular smooth muscle? Med Hypoth 5: 843-848.
9. Turlapaty PDMV, Altura BM (1980) Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. Science 208: 198-200.
10. Kimura T, Yasue H, Sakaino N, Rokutanda M, Jougasaki M, et al. (1989) Effects of magnesium on the tone of isolated human coronary arteries. Circulation 79: 118-1124.
11. Goto K, Yasue H, Okumura K (1990) Magnesium deficiency detected by intravenous loading test in variant angina pectoris. Am J Cardiol 65: 709-712.
12. Simko F (1994) Pathophysiological aspects of the protective effect of magnesium in myocardial infarction. Acta Med Hung 50: 55-64.
13. Satake K, Lee JD, Shinizu H, Ueda T, Makamura T (1996) Relation between severity of magnesium deficiency and frequency of angina attacks in men with variant angina. J Am Coll Cardiol 28: 897-902.
14. Sueda S, Fukuda H, Watanabe K (2001) Magnesium deficiency in patients with recent myocardial infarction and provoked coronary artery spasm. Jap Circ J 65: 643-648.
15. Minato N, Katayama Y, Sakaguchi M, Itoh M (2006) Perioperative coronary artery spasm in off-pump coronary bypass grafting and its possible relation with perioperative hypomagnesemia. An Thorac Cardiovasc Surg 12: 32-36.
16. Altura BM, Altura BT, Carella A, Turlapaty PD (1981) Hypomagnesemia and vasoconstriction: Possible relationship to etiology of sudden death ischemic heart disease and hypertensive vascular disease. Artery 9: 212-231.
17. Whang R, Aikawa JR, Oei TO, Hamiter T (1980) Routine serum magnesium determination-an unrecognized need. In: Magnesium in Health and Disease. SP Med & Scient Bks, New York. pp: 1-5.
18. Whang R, Chrysant S, Dillard B, Smith W, Fryer A (1982) Hypomagnesemia and hypokalemia in 1,000 treated ambulatory patients. J Am Coll Nutr 1: 317-322.
19. Sheehan J, White A (1982) Diuretic-associated hypomagnesemia. Brit Med J 285: 1157-1159.
20. Whang R, Oei TO, Watanabe A (1984) Frequency of hypomagnesemia in hospitalized patients receiving digitalis. Arch Int Med 145: 655-656.
21. Altura BM, Altura BT (1985) New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. I. Clinical aspects. Magnesium 4: 226-244.
22. Rude RK, Singer FR (1981) Magnesium deficiency and excess. Annu Rev Med 32: 245- 259.
23. Ryzen E, Wagner PW, Singer FR, Rude RK (1985) Magnesium deficiency in a medical ICU population. Critical Care Med 13: 19-21.
24. Whang R (1987) Magnesium deficiency: Pathogenesis, prevalence, and clinical implications. Am J Med 82: 24-29.
25. Salem M, Muiz R, Chernow B (1991) Hypomagnesemia in critical illness: A common and critically important problem. Crit Care Med 7: 225-252.
26. Altura BM, Lewenstam A (1994) Unique magnesium –sensitive ion selective electrodes. Scand J Clin Lab Invest 54: 1-100.
27. Altura BT, Altura BM (1991) Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. Magnes trace Elem 10: 90-98.
28. de baaj JHF, Henderop JG, Bindels RJ (2015) Magnesium in man: Implications for health and disease. Physiol Rev 95: 1-46.
29. Altura BM, Altura BT (1984) Magnesium, electrolyte transport and coronary vascular tone. Drugs 28: 120-142.
30. Altura BM, Altura BT (1985) New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. Experimental aspects. Magnesium 4: 245-271.
31. Altura BM, Altura BT (1990) Magnesium and the cardiovascular system: Experimental and clinical aspects updated. Metals in Biological Systems 26: 359-416.
32. Altura BM, Altura BT (1995) Magnesium and cardiovascular biology: An important link between cardiovascular risk factors and atherogenesis. Cell Mol Biol Res 41: 347-359.
33. Seelig MS, Rosanoff A (2003) The magnesium factor. The Penguin Group, New York.
34. Altura BM, Altura BT (2007) Magnesium: Forgotten mineral in cardiovascular biology and angiogenesis. New Perspectives in Magnesium Research. Springer, London, UK. pp: 239-260.
35. Altura BM, Shah NC, Shah GJ, Altura BT (2016) Genotoxic effects of magnesium deficiency in the cardiovascular system and their relationships to cardiovascular diseases and atherogenesis. J Cardiovasc Dis Diagn S1: 1-008.
36. Saris NR, Mervaala E, Karppanen H, Lewenstam A (2000) Magnesium: An update on physiological, clinical and analytical aspects. Clin Chim Acta 294: 1-26.
37. Altura BM, Shah NC, Shah GJ, Perez-Albela JL, Altura BT (2016) Magnesium deficiency results in oxidation and fragmentation of DNA, downregulation of telomerase activity, and ceramide release in cardiovascular tissues and cells: Potential relationship to atherogenesis, cardiovascular diseases and aging. Int J Diabetol & Vasc Dis res 4: 1-5.
38. Shah NC, Shah GJ, Li W, Altura BT, Altura BM (2017) Short-term magnesium deficiency upregulates RIPK3 in cardiovascular tissues and cells: cross-talk with cytokines, acid sphingomyelinase and ceramide.

39. Marier JR (1982) Quantitative factors regarding magnesium status in the modern-day world. Magnesium 1: 3-15.

40. Ford ES, Mokdad AH (2003) Dietary magnesium in a national sample of US adults. J Nutr 133: 2879-2882.

41. Mosdegh A, Goldman J, Abuja J, Rhodes D, La Comb R (2009) What we eat in America, NHANES 2005-2006: Usual intakes from food and water compared to 1997 dietary reference intakes for vitamin d, calcium, phosphorus, and magnesium. US Department of Agricultural Research Service, Washington, DC.

42. NHANES (2017) Dietary reference intakes for vitamin d, calcium, phosphorus, and magnesium. US Department of Agricultural Research Service, Washington, DC.

43. Altura BT, Altura BM (1994) A method for distinguishing ionized, complexed and protein-bound Mg in normal and diseased human plasma. Scand J Clin Lab Invest 54: 83-87.

44. Altura BT, Shirey TL, Young CC, Hii J, Dell'Orfano K, et al. (1992) A new method for the rapid determination of ionized Mg^{2+} in whole blood, serum and plasma. Methods Find Exp Clin Pharmacol 14: 297-304.

45. Altura BT, Shirey TL, Young CC, Dell'Orfano K, Altura BM (1992) Characterization and studies of a new ion selective electrode for free extracellular magnesium ions in whole blood, plasma and serum. In: D'Orazio P, Buritt M, Sena SF (eds.), Electrolytes, blood gases, and other critical analytes: The patient, the measurement, and the government. Omni Press, Madison. pp: 152-173.

46. Altura BM, Altura BT (2016) Importance of ionized magnesium measurements in physiology and medicine and the need for ion-selective electrodes. J Clin Case Studies.

47. Altura BM, Altura BT (1974) Magnesium and contraction of arterial smooth muscle. Microvasc Res 7: 145-155.

48. Altura BM, Altura BT (1978) Magnesium and vascular tone and reactivity. Blood Vessels 15: 5-16.

49. Altura BM (1978) Magnesium withdrawal and rhythmic contractility of arterial and venous smooth muscle: Differential effects of multivalent cations and EDTA. Artery 4: 512-527.

50. Altura BT, Altura BM (1980) Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries. Neurosci Lett 20: 323-327.

51. Altura BM, Altura BT (1981) Magnesium modulates calcium entry in vascular smooth muscle. In: Onishi T, Endo M (eds.), The Mechanisms of Gated Calcium transport Across Biological Membranes. Academic Press, USA.

52. Altura BM, Altura BT (1981) Role of magnesium ions in contractility of blood vessels and skeletal muscles. Magnesium Bull 3: 102-114.

53. Altura BM, Altura BT (1981) General anesthetics and magnesium ions as calcium antagonists. In: GB Weiss (ed.), New Perspectives on Calcium Antagonists. Am Physiol Soc, pp: 131–145.

54. Turlapaty PDMV, Weiner R, Altura BM (1981) Interactions of magnesium and verapamil on tone and contractility of vascular smooth muscle. Eur J Pharmacol 74: 263-272.

55. Altura BM, Turlapaty PDMV (1982) Withdrawal of magnesium enhances coronary arterial spasms produced by vasoactive agents. Br J Pharmacol 77: 649-659.

56. Altura BM, Altura BT, Carella A, Turlapaty PDMV (1982) Ca^{2+} coupling in vascular smooth muscle: Mg^{2+} and buffer effects on contractility and membrane Ca^{2+} movements. Canad J Physiol Pharmacol 60: 459-482.

57. Altura BM, Altura BT, Carella A (1983) Magnesium deficiency-induced spasms of umbilical vessels: relation to preeclampsia, hypertension, growth retardation. Science 221: 376-378.

58. Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, et al. (1987) Mg^{2+} -Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Canad J Physiol Pharmacol 65: 729-745.

59. Murakawa T, Altura BT, Altura BM (1988) Importance of magnesium and potassium concentration on basal tone and 5-HT induced contractions in canine coronary artery. Br J Pharmacol 94: 325-334.

60. Murakawa T, Altura BT, Altura BM (1990) Extracellular magnesium and potassium concentrations interact to modulate tone and reactivity of isolated canine cerebral vascular muscle. Magnesium 9: 79-93.

61. Zhang A, Carella A, Altura BT, Altura BM (1991) Interactions of magnesium and chloride ions on tone and contractility of vascular muscle. Eur J Pharmacol 203: 223-235.

62. Zhang A, Cheng TPO, Altura BM (1992) Magnesium regulates intracellular free calcium and contraction and cell geometry in vascular smooth muscle cells. Biochim Biophys Acta 1134: 25-29.

63. Yang ZW, Wang J, Altura BT, Altura BM (2000) Extracellular magnesium deficiency induces contraction of arterial muscle: role of PI3 kinases and MAPK signaling pathways. Pflug Arch 439: 240-247.

64. Yang ZW, Wang J, Zheng T, Altura BT, Altura BM (2000) Low extracellular Mg^{2+} induces contraction and $[Ca^{2+}]_i$ rises in cerebral arteries: roles of Ca^{2+} , PKC and PI-3 kinases. Am J Physiol Heart Circ Physiol 279: H2898-29007.

65. Altura BM, Altura BT, Gupta RK (1992) Alcohol intoxication results in rapid loss in free magnesium and disturbances in brain bioenergetics: relation to cerebrovasospasm, alcohol-induced strokes, and barbiturate anesthesia induced deaths. Magnes Trace Elem 10: 122-135.

66. Itura BM, Zhang A, Cheng TP-O, Altura BM (1993) Ethanol promotes rapid depletion of intracellular free Mg in cerebral vascular smooth muscle cells: possible relation to alcohol-induced behavioral and stroke-like effects. Alcohol 10: 563-566.

67. Altura BM, Altura BT (1994) Role of magnesium and calcium in alcohol-induced hypertension and strokes as probed by in-vivo television microscopy, digital image microscopy, optical spectroscopy, 31P-NMR spectroscopy and a unique magnesium ion-selective electrode. Alcohol: Clin Exp res 18: 1057-1068.

68. Altura BM, Gebrewold A, Altura BT, Gupta RK (1995) Role of brain $[Mg^{2+}]_i$ in alcohol-induced hemorrhagic stroke in a rat model. A 31P-NMR in-vivo study. Alcohol 12: 131-136.

69. Altura BM, Zhang A, Cheng TP-O, Altura BT (1995) Alcohols induce rapid depletion of intracellular free Mg^{2+} in cerebral vascular muscle cells: Relation to chain length and partition coefficient. Alcohol 12: 247-250.

70. Altura BM, Altura BT, Begleiter H, Kissin B (1996) Effects of alcohol on brain circulation. In: The Pharmacology of Alcohol and Alcohol Dependence. Oxford Univ Press. pp: 181-206.

71. Altura BM, Weaver C, Gebrewold A, Altura BT, Gupta RK (1998) Continuous osmotic pump infusion of alcohol into brain decreases brain $[Mg^{2+}]_i$ and brain bioenergetics and enhances susceptibility to hemorrhagic stroke mortality induced by alcohol: An in-vivo study. Alcohol 15: 112-117.

72. Babu AT, Cheng TP-O, Zhang A, Altura BT, Altura BM (1999) Low concentrations of ethanol deplete type-2 astrocytes of intracellular free magnesium. Brain Res Bull 50: 59-62.

73. Li W, Zheng T, Altura BT, Altura BM (1999) Magnesium modulates contractile responses of rat aorta to thiocyanate: a possible relationship to smoking-induced atherosclerosis. Toxicol Appl Pharmacol 157: 77-84.

74. Dean C (2014) The magnesium miracle (3rd edn.). Ballantine Books, New York.

75. Altura BM (1988) Ischemic heart disease and magnesium. Magnesium 7: 57-67.

76. Altura BM, Altura BT (1971) Influence of magnesium on drug-induced contractions and ion content in rabbit aorta. Am J Physiol 220: 938-944.

77. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T (1984) Magnesium deficiency and hypertension: correlation between magnesium deficiency diets and microcirculatory changes in situ. Science 223: 1315-1317.

78. Altura BT, Brust M, Bloom S, Barbour RL, Stempak J, et al. (1990) Magnesium dietary intake modulates blood lipid levels and atherogenesis. Proc Nat Acad Sci USA 87: 1840-1844.

79. Altura BM, Altura BT (1996) Magnesium as an extracellular signal in cardiovascular pathobiology. J Jap Soc Magnes Res 15: 17-32.

80. Altura BM, Altura BT, Casteels R, Godfraind T, Ruegg JC (1977) Extracellular magnesium and contraction of vascular smooth muscle. In: Excitation-Contraction Coupling of Smooth Muscle. North-Holland Publ Co., Amsterdam. pp: 137-144.

81. Wu F, Altura BT, Gao J, Barbour RL, Altura BM (1994) Ferrylmyoglobin formation induced by acute magnesium deficiency in perfused rat heart causes cardiac failure. Biochim Biophys Acta 1225: 158-164.

82. Altura BM, Barbour RL, Dowd TL, Wu F, Altura BT, et al. (1993) Low extracellular magnesium induces intracellular free Mg^{2+} deficits, ischemia, depletion of high-energy phosphates and cardiac failure in intact working rat hearts: A 31P-NMR

study. Biochim Biophys Acta 1182: 329-332.

83. Altura BM, Gebrewold A, Altura BT, Brautbar N (1996) Magnesium depletion impairs carbohydrate and lipid metabolism and cardiac bioenergetics and raises myocardial calcium content in vivo: relationship to etiology of cardiac diseases. Biochem Mol Biol Int 40: 1183-1190.

84. Altura BM, Kostellow AB, Zhang A, Li W, Morrill GA, et al. (2003) Expression of the nuclear factor-kB and proto-oncogenes c-fos and c-jun are induced by low extracellular Mg^{2+} in aortic and cerebral vascular smooth muscle cells: possible links to hypertension, atherogenesis and stroke. Am J Hypertens 16: 347-359.

85. Morrill GA, Gupta RK, Kostellow AB, Ma GY, Zhang A, et al. (1997) Mg^{2+} modulates membrane lipids in vascular smooth muscle cells: a link to atherogenesis. FEBS Lett 408: 191-194.

86. Morill GA, Gupta RK, Kostellow AB, Ma GY, Zhang A, et al. (1998) Mg^{2+} modulates membrane sphingolipids and lipid messengers in vascular smooth muscle cells. FEBS Lett 440: 167-171.

87. Altura BM, Shah NC, Jiang XC, Perez-Albela JL, Sica AC, et al. (2009) Short-term magnesium deficiency results in decreased levels of serum sphingomyelin, lipid peroxidation, and apoptosis in cardiovascular tissues. Am J Physiol Heart Circ Physiol 297: H86-H92.

88. Altura BM, Shah NC, Li Z, Jiang XC , Perez-Albela JL, et al. (2010) Magnesium deficiency upregulates serine palmitoyl transferase (SPT 1 and SPT 2) in cardiovascular tissues: Relationship to ionized Mg^{2+} and cytochrome C. Am J Physiol Heart Circ Physiol 299: H932-H938.

89. Shah NC, Liu JP, Iqbal J, Hussain M, Jiang XC, et al. (2011) Mg deficiency results in modulation of serum lipids, glutathione and NO synthase isozyme activation in cardiovascular tissues: relevance to *de novo* synthesis of ceramide, serum Mg and atherogenesis. Int J Clin Exp Med 4: 103-118.

90. Zheng T, Li W, Altura BT, Shah NC, Altura BM (2011) Sphingolipids regulate $[Mg^{2+}]_0$ uptake and $[Mg^{2+}]_i$ content in vascular smooth muscle cells: Potential mechanisms and importance to membrane transport of Mg^{2+}. Am J Physiol Heart Circ Physiol 300: H486- H492.

91. Altura BM, Shah NC, Shah GJ, Zhang A, Li W, et al. (2012) Short-term magnesium deficiency upregulates ceramide synthase in cardiovascular tissues and cells: Cross-talk among cytokines, Mg^{2+} , NF-kB and *de novo* ceramide. Am J Physiol Heart Circ Physiol 302: 319-332.

92. Altura BM, Li W, Zhang A, Shah NC, Shah GJ, et al. (2016) The expression of platelet activating-factor is induced by low extracellular Mg^{2+} in aortic, cerebral and neonatal coronary vascular smooth muscle; cross-talk with ceramide production, NF-kB and proto-oncogenes: possible links to atherogenesis and sudden cardiac death in children and infants, and aging: Hypothesis, review and viewpoint. Int J Cardiol Res 3: 47-67.

93. Altura BM, Shah NC, Shah GJ, Li W, Zhang A, et al. (2013) Magnesium deficiency upregulates sphingomyelinases in cardiovascular tissues and cells: cross-talk among proto-oncogenes, Mg^{2+} ,NF-kB, and ceramide and their potential relationships to resistant hypertension, atherogenesis and cardiac failure. Int J Clin Exp Med 6: 861-879.

94. Shah NC, Shah GJ, Li W, Jiang XC, Altura BT, et al. (2014) Short-term magnesium deficiency downregulates telomerase, upregulates neutral sphingomyelinase and induces oxidative damage in cardiovascular tissues: relevance to atherogenesis, cardiovascular diseases and aging. Int J Clin Exp Med 7: 497-514.

95. Altura BM, Shah NC, Shah GJ, Altura BT (2016) Genotoxic effects of magnesium deficiency in the cardiovascular system and their relationships to cardiovascular diseases and atherogenesis. J Cardiovasc Dis Diagnosis S1: 008.

96. Altura BM, Gebrewold A, Shah NC, Shah GJ, Altura BT (2016) Potential roles of magnesium deficiency in inflammation and atherogenesis: Importance and cross-talk of platelet activating-factor and ceramide. J Clin Exp Cardiol 7: 427.

97. Altura BM, Shah NC, Shah GJ, Perez-Albela JL, Altura BT (2016) Insights into the possible mechanisms by which platelet activating-factor and PAF-receptors function in vascular smooth muscle in magnesium deficiency and vascular remodeling: possible links to atherogenesis, hypertension and cardiac failure. Int J Cardiol Res 3: 1-3.

98. Altura BM, Li W, Zhang A, Shah NC, Shah GJ, et al. (2016) Sudden cardiac death in infants, children and young adults: possible roles of dietary magnesium intake and generation of platelet activating0factor in coronary arteries. J Heart Health 2.

99. Merrill AH, Jones DD (1990) An update of the enzymology and regulation of sphingolipid metabolism. Biochim Biophys Acta 1044: 1-12.

100. Haimovitz-Friedman A, Kolesnick RN, Fuchs Z (1997) Ceramide signaling in apoptosis. Br Med Bull 53: 539-553.

101. Hannun YA, Obeid LM (2002) The ceramide-centric universe of lipid – mediated cell regulation: stress encounters of the lipid kind. J Biol Chem 277: 25847-25850.

102. Auge N, Negre-Salvayre R, Levade T (2000) Sphingolipid and metabolites in vascular signaling and atherosclerosis. Progr Lipid Res 39: 207-229.

103. Panday S, Murphy RE (2007) Recent advances in the immunobiology of ceramide. Exp Mol Pathol 82: 296-309.

104. Pascual M, Valles SL, Renau-Piqueras J, Guerri C (2003) Ceramide pathways modulate ethanol-induced cell death. J Neurochem 87: 1535-1545.

105. Bielawska AE, Shapiro JP, Jiang L, Melkonyan HS, Piot C, et al. (2016) Ceramide (is involved in triggering of cardiomyocyte apoptosis induce by ischemia and reperfusion. Am J Pathol 151: 1257-1263.

106. Altura BM, Altura BT (1995) Magnesium in cardiovascular biology. Sci Am Sci & Med 2: 28-37.

107. Zheng T, Li W, Wang J, Altura BT, Altura BM (1999) Ceramide attenuates phenylephrine-induced vasoconstriction and elevation in $[Ca^{2+}]_i$ in rat aortic smooth muscle. Lipids 34:689-695.

108. Zheng T, Li W, Wang J, Altura BT, Altura BM (1999) Effects of neutral-sphingomyelinase on phenylephrine-induced vasoconstriction and Ca^{2+} mobilization in rat aortic smooth muscle. Eur J Pharmacol 391: 127-135.

109. Zheng T, Li W, Wang J, Altura BT, Altura BM (2000) Sphingomyelinase and ceramide analogs induce contraction and rises of $[Ca^{2+}]_i$ in canine cerebral vascular smooth muscle. Am J Physiol Heart Circ Physiol 278: 1421-1428.

110. Altura BM, Gebrewold A, Zheng T, Altura BT (2002) Sphingomyelinase and ceramide analogs induce vasoconstriction and leukocyte interactions in cerebral venules in the intact rat brain: insight into the mechanisms and possible relation to brain injury and stroke. Brain Res Bull 58: 271-278.

111. Williams RD, Sgoutas DS, Zaatari GS (1986) Enzymology of long-chain base synthesis by aorta: induction of serine palmitoyltransferase activity in rabbit aorta during atherogenesis. J Lipid Res 27: 763-770.

112. Hanada K, Hara T, Nishikjima M, Kuge O, Dickson RC (1997) A mammalian homolog of the yeast LCB1 encodes a component of serine palmitoyltransferase, the enzyme catalyzing the first step in sphingolipid biosynthesis. I Biol Chem 272: 32108-32114.

113. Weiss B, Stoffel W (1997) Human and murine serine-palmitoyl-CoA transferase-cloning expression and characterization of the key enzyme in sphingolipid synthesis. Eur J Biochem 249: 239-247.

114. Yasuda S, Nishijima M, Hanada K (2003) Localization, topology, and function of the LCB1 subunit of serine palmitoyltransferase in mammalian cells. J Biol Chem 278: 4176-4183.

115. Hanada K (2003) Serine palmitoyltransferase, a key enzyme of sphingolipid metabolism. Biochim Biophys Acta 1632:16-30.

116. Krysko DV, Kaczmarek A, Vandenbeele P (2009) Molecular pathways of different types of cell death: Many roads to cell death. In: Phagocytosis of dying cells from molecular mechanisms to human disease. Springer, New York. pp: 4-31.

117. Majno G, Joris I (2004) Cells, tissues, and disease: Principles of general pathology. Oxford University Press, UK. pp: 307-524.

118. Kumar V, Abbas AK, Aster JC (2015) Robbins and cotran pathologic basis of disease. Elsevier-Saunders, Phialdelphia. pp: 496-501.

119. Altura BM, Shah NC, Li Z, Jiang XC, Zhang A, et al. (2010) Short-term magnesium deficiency upregulates sphingomyelin synthase and p53 in cardiovascular tissues and cells; relevance to the *de novo* synthesis of ceramide. Am J Physiol Heart Circ Physiol 296: 2046-2055.

120. Altura BM, Shah NC, Shah GJ, Zhang A, Li W, et al. (2014) Short-term Mg deficiency upregulates protein kinase C isoforms in cardiovascular tissues and cells: relation to NF-kB, cytokines, ceramide salvage sphingolipid pathway and PKC-zeta: Hypothesis and review. Int J Clin Exp Med 7: 1-21.

121. Yang ZW, Wang J, Zhang A, Altura BT, Altura BM (2000) Low $[Mg^{2+}]_0$ induces contraction of cerebral arteries: roles of tyrosine and mitogen-activated protein kinases. Am J Physiol Heart Circ Physiol 279: 185-194.

122. Altura BM, Altura BT (2009) Atherosclerosis and magnesium. In: calcium and magnesium in drinking water. Public Health Significance WHO, Geneva. pp: 75-78.